Kinetic Studies of Fast Equilibrium by Means of High-Performance Liquid Chromatography. XIV.[1] Separation of Rotamers of Phenyl Methylcarbamates and Their Rotational Energy Barriers

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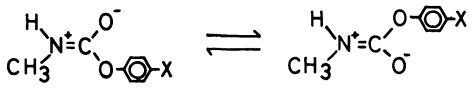
High-performance liquid chromatography(HPLC) of six phenyl methylcarbamates at low column temperatures on normal phase chromatography using hydroxyl-group chemically-bonded silica gel packing achieved the separation of rotamers. The population ratios of rotamers were determined for different conditions such as solvent composition and concentration. The rotational-energy barriers to intramolecular-bond rotation about the carbonyl–nitrogen bonds were determined for four *p*-substituted phenyl methylcarbamates, and it was found that the energy barriers were higher when electron-withdrawing groups were substituted.

In this research series, rotamers about the carbon–nitrogen bonds with partial double-bond characters, including metal dithiocarbamates,[2] anilides,[3–5] and *N*-alkylamides,[1] have been separated by means of HPLC at low column temperatures. The population ratios of rotamers in different conditions have been determined by this method, and the energy barriers to bond rotations have also been determined. This report deals with the separation of rotamers of *p*-substituted phenyl methylcarbamates and the determination of their rotational-energy barriers.[6]



cis(Z) trans(E)

The restricted rotation about the carbonyl–nitrogen bonds of amides has been extensively investigated by many workers by means of NMR[7] with a special technique entitled the dynamic NMR method. Our previous reports[1,3–5] have demonstrated that HPLC has also been a powerful tool for examining the restricted bond rotation of amides and even better than NMR when the content of the minor rotamers is very low. Different from amides, the number of reports on dynamic NMR studies of carbamates is relatively few and they are restricted to symmetrical *N,N*-disubstituted carbamates. These are attributable to the following. (1) Different from amides, the differences in chemical shifts of two rotamers of carbamates are usually very small. This makes dynamic NMR studies of carbamates very difficult and once led to an erroneous conclusion that, different from amides, there were no large energy barriers to the carbonyl–nitrogen bond rotation of carbamates.[8] This difficulty was partially resolved by the use of a large amount of lanthanoid shift reagents; thus, the rotational-energy barriers were determined for dimethylcarbamates.[9] It is debatable, however, whether the rotational-energy barriers in the absence and presence of shift reagents are identical since it is probable that interactions between the shift reagents and carbamate molecules cause a variation in the energy barriers as well as the population ratios to a considerable extent. In addition, other difficulties exist for *N*-monosubstituted carbamates. (2) For symmetrically *N,N*-disubstituted carbamates, due to the equal population ratios of "two rotamers" simple T_c method[10] can be applied to determine the energy barriers. Contrary to this, complicated total line-shape analysis is inevitable for unsymmetrically *N*-substituted carbamates. The proximity of chemical shifts of two rotamers not only makes the total line-shape analysis impossible, but also prevents a determination of the population ratios of two rotamers. (3) Owing to a strong intermolecular association, such as the hydrogen bonding of *N*-monosubstituted carbamates, the overall process observed by means of NMR might involve the making and breaking of hydrogen bonds as well as bond rotation. Thus, it is not clear that the data obtained by means of dynamic NMR correctly indicate the rotational energy barriers, even though a total line-shape analysis is possible. For these reasons, a determination of the rotational-energy barriers has not hitherto been carried out for *N*-monosubstituted carbamates.

Experimental

The following six *p*-substituted phenyl methylcarbamates were prepared and purified as described elswhere;[11] phenyl methylcarbamate, *p*-methylphenyl methylcarbamate, *p*-fluorophenyl methylcarbamate, *p*-nitrophenyl methylcarbamate, *p*-hydroxyphenyl methylcarbamate, and *p*-cyanophenyl methylcarbamate.

The HPLC apparatus for use in low-temperature measurements was detailed elswhere.[3,12] Several column packings of two different types, i.e., silica-gel packings (LiChrosorb SI 60, LiChrosorb SI 100, and Polygosil 60-5)

and hydroxyl-group chemically-bonded packings (LiChrosorb DIOL and Nucleosil 7OH), were tested and it was found out that the latter gave better results. Complete base-line separation of rotamers by silica-gel packings was difficult because the retention times of rotamers were relatively close to each other. For the determination of the population ratios of rotamers, column effluent was passed through a narrow stainless-steel tube (0.5 mm in internal diameter and 10 m in length) which was thermostated at 80 °C in an air bath prior to detection by means of UV detector.[4] Thus, the equilibrium of rotamers in eluent was reequilibrated.

Results and Discussion

Separation of Rotamers. These six phenyl methylcarbamates were dissolved in chloroform or ethanol (0.01 mol dm^{-3}), and sample solutions were submitted to normal phase HPLC at different column temperatures. Figure 1 exemplifies the chromatograms of phenyl methylcarbamate in a chloroform solution on hydroxyl-group chemically-bonded packings. Two peaks corresponding to two rotamers appeared and were separated at low column temperatures. A complete base-line separation of rotamers was attained when the column temperature was below −55 °C, although the column efficiency gradually decreased with the falling temperature. With similar procedures, the separation of rotamers of other *p*-substituted phenyl methylcarbamates was possible below −55 °C.

The identification of each peak was not easy because different from anilides and amides hitherto NMR were not available. We consider, however, that the former small peak will be attributable to the cis-form (*Z*-form) for the following reason. Owing to the ability to form ring dimer,[13] the dielectric constants of cis-form (*Z*-form) rotamers of amides and carbamates are much smaller than those of trans-form (*E*-form) rotamers.[14] It is a well-known fact that in the adsorption or normal phase partition chromatography, nonpolar species are eluted faster than polar ones. This was actually observed for anilides and *N*-alkylamides as can be seen in our previous reports.[1,3,4] It is quite likely that a similar elution sequence can also be observed for carbamates. Hereafter, it is assumed that the former small peak can be assigned as cis-form (*Z*-form), although some ambiguity still remains on the peak identification.

Equilibrium Ratios of Rotamers. The ratios of two rotamers in chloroform and in ethanol were determined for these six carbamates (0.01 mol dm^{-3}, 25 °C), and the results are summarized in Table 1. For *p*-methylphenyl methylcarbamate, the ratios of two rotamers were determined in a variety of solvents (0.01 mol dm^{-3}, 25 °C), and the percentages of cis-form (*Z*-form) are determined which are as follows: 24% (in hexane), 22% (in benzene), 29% (in carbon tetrachloride), 14% (in diethyl ether), 14% (in ethyl acetate), 14% (in acetonitrile), 13% (in tetrahydrofuran), and 14% (in methanol). The effect of the concentration was also examined for *p*-methylphenyl methylcarbamates in chloroform. The percentages of cis-form (*Z*-form) were as follows; 17% (3.0 mol dm^{-3}), 22% (0.1 mol dm^{-3}), and 24% (0.01 mol dm^{-3}). By summarizing these results it can be concluded that the percentages of cis-form (*Z*-form) of these carbamates are higher in nonpolar solvents and in lower concentrations which is similar to the case for

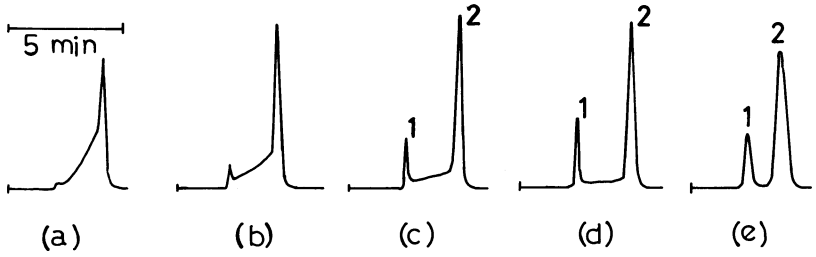


Fig. 1. HPLC chromatograms of phenyl methylcarbamate at various temperatures.
Column: Nucleosil 7OH (4.6 mm × 15 cm). Eluent: hexane: 1-propanol: acetic acid = 100 : 10 : 3, 2.5 cm^3 min. Detector: UV 254 nm. (a): −25 °C, (b): −30 °C, (c): −35 °C, (d): −40 °C, (e): −55 °C. 1 cis-form(*Z*-form), 2 trans-form(*E*-form).

Table 1. Percentage of Phenyl Methylcarbamates Existing as cis-Form (*Z*-Form) in Chloroform and Ethanol

	X					
	H	CH_3	OCH_3	NO_2	F	CN
In 0.01 mol dm^{-3} chloroform	23	24	26	13	21	15
In 0.01 mol dm^{-3} ethanol	19	17	17	8.8	16	7.4

25 °C.

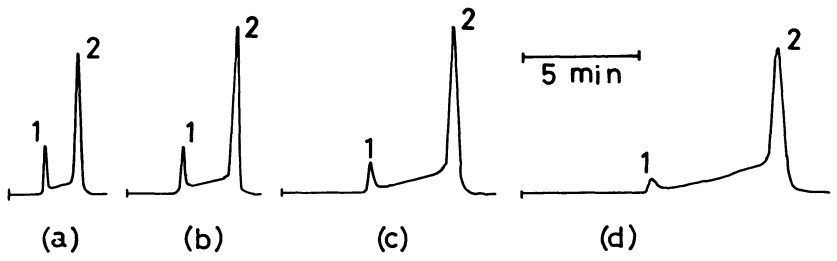


Fig. 2. HPLC chromatograms of phenyl methylcarbamate at −35 °C in different flow rate. Column: Nucleosil 7OH (4.6 mm × 15 cm). Eluent: hexane: 1-propanol: acetic acid = 100 : 10 : 3. Detector: UV 254 nm. Column temperature: −35 °C. Flow rate; (a): 4.3 $cm^3\ min^{-1}$, (b): 2.5 $cm^3\ min^{-1}$, (c): 1.4 $cm^3\ min^{-1}$, (d): 0.8 $cm^3\ min^{-1}$.

anilides and aliphatic amides.[1,4]

Determination of Rotational Energy Barriers. As described above, HPLC of phenyl methylcarbamates gave the separation of rotamers below −55 °C. Under the conditions of a baseline separation of rotamers, each peak was symmetrical and neither leading nor tailing was observed. With an increase in the column temperature, a partial transformation between two rotamers took place during the course of chromatography. In this case, complicated chromatograms were obtained. An approximate HPLC method for the determination of rotational-energy barriers[5] can be applied by observing the change in chromatographic patterns, provided that the rotational energy barriers are little affected by the adsorption or partition process of solute molecules on column packings. Figure 2 exemplifies the chromatograms of phenyl methylcarbamate at a column temperature of −35 °C for different flow rates. When the flow rate was low, a larger part of one rotamer transformed into other rotamer during the course of chromatography. The residual amount of cis-form (*Z*-form) was proportional to the product of the peak area of cis-form *S* and the flow rate *v* at a residence time *t* was plotted against *t*. Similar experiments were carried out at different column temperatures and the results are given in Fig. 3. From the slope of these linear curves, the rate constants to the bond rotation from cis-form (*Z*-form) to trans-form (*E*-form) k at different temperatures were calculated. The reverse rate constants k corresponding to the conversion from trans-form (*E*-form) to cis-form (*Z*-form) were also determined by the same way. The rate constants k and k_- for other carbamates including *p*-methylphenyl methylcarbamate, *p*-methoxyphenyl methylcarbamate, and *p*-nitrophenyl methylcarbamate were also determined with similar procedures. The activation energies of the forward E_a (from cis- to trans-form) and backward E_{-a} (from trans- to cis-form) reactions were calculated from the Arrhenius' plots as shown in Fig. 4. Thus, activation energies as well as rate constants can be determined. Table 2 summarizes the activation

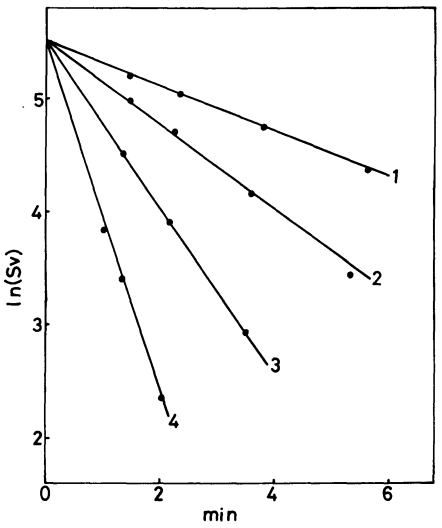


Fig. 3. Plots of residual amount of cis-form (*Z*-form) of phenyl methylcarbamate vs. residence time. 1: −40 °C, 2: −35 °C, 3: −30 °C, 4: −25 °C.

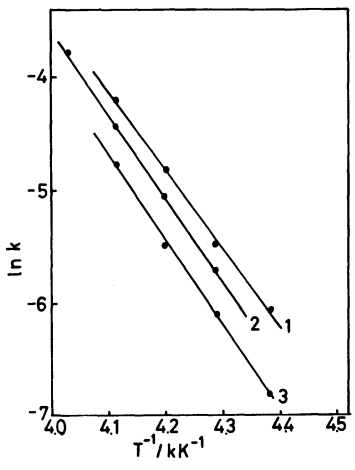


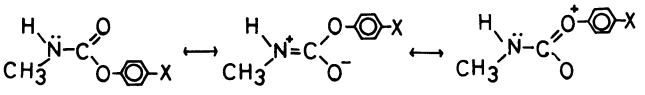
Fig. 4. Arrhenius' plot of intramolecular carbonyl-nitrogen bond rotation of phenyl methylcarbamates. 1: *p*-methoxyphenyl methylcarbamate, 2: phenyl methylcarbamate, 3: *p*-nitrophenyl methylcarbamate.

Table 2. Rate Constants and Energy Barriers of the Bond Rotation of Phenyl *N*-Methylcarbamates

	k(s^{-1}) at −30 °C trans→cis	k_{-}(s^{-1}) at −30 °C cis→trans	E_a(kJ mol^{-1}) cis→trans	E_{-a}(kJ mol^{-1}) trans→cis
p-Methoxyphenyl methylcarbamate	1.5×10^{-2}	1.2×10^{-3}	56.5	50.2
p-Methylphenyl methylcarbamate	1.3×10^{-2}	1.2×10^{-3}	59.0	53.2
Phenyl methylcarbamate	1.2×10^{-2}	1.0×10^{-3}	62.4	58.2
p-Nitrophenyl methylcarbamate	8.5×10^{-3}	*	64.4	*

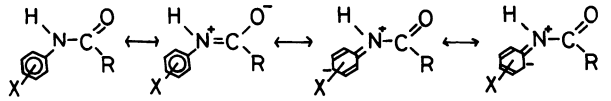
* Due to the tailing of trans-form (*E*-form) rotamer, the rate constants and energy barriers of the reverse reaction were not calculated.

energies and rate constants at −30 °C for these four phenyl methylcarbamates. These energy barriers were found to be smaller than those of aliphatic amides[7] and close to those of anilides.[5,7] When a hydrogen in *p*-position in phenyl ring is replaced by an electron-withdrawing group, rotational energy barriers increase. On the other hand, the substitution by an electron-donating group decreases the energy barriers. These phenomena are explained by the following way. The contribution of the canonical form 2, which is responsible for the partial double



1 2 3

bond character of carbonyl-nitrogen bonds, is reduced by the contribution of another canonical form 3 for carbamates. Thus, the rotational energy barriers of carbamates are usually smaller than those of alkylamides. Similarly, the partial double bond character of carbonyl-nitrogen bonds of anilides is also reduced by dint of the contribution of the canonical forms 6 and 7. The substitution of a



4 5 6 7

hydrogen atom in phenyl group by substituent X will bring about reverse effects on the rotatinal energy barriers for carbamates and anilides. In the case of anilides, the substitution of *o*- or *p*-hydrogen by an electron-donating group such as methoxy group will destabilize the canonical forms 6 and 7, and consequently the substitution will bring about an increase in the double-bond character and, thus, an increase in the energy barriers. Contrary to this, the substitution by an electron-withdrawing group such as nitro group will cause a decrease in the energy barriers. This phenomenon was actually observed by a dynamic NMR study for *p*-substituted *N*-methylformanilides.[15] The rotational energy barreirs of *p*-nitro-substituted *N*-methylformanilide and *p*-methoxy-substituted *N*-methylformanilide were 71.5 and 78.5 kJ mol^{-1}, respectively. The effects of substituents should differ for carbamates. The replacement of a hydrogen in the phenyl ring of phenyl methylcarbamates by an electron-donating group should stabilize the canonical form 3 and, thus, decreases the double-bond character of the carbonyl–nitrogen bonds. This is in agreement with the present experiments.

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6) Due to the strong double bond character of the carbonyl nitrogen bond, moiety is considered to lie on the same plane. In this report the prefixes cis- and trans- designate the configuration concerning C–O^- and N–H groups because the configuration seems to play an essential role. The alternative prefixes, *E*- and *Z*-, which were used for amides in our previous reports (Ref. 1,3,4, and 5), were shown in parentheses in this report because *Z*- and *E*-mean reverse configuration concerning C–O^- and N–H groups for amides and carbamates.

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